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Asthma across the ages: Knowledge gaps in childhood asthma

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The Eunice Kennedy Shriver National Institute of Child Health and Human Development convened an Asthma Group in response to the Best Pharmaceuticals for Children Act. The overall goal of the Best Pharmaceuticals for Children Act Program is to improve pediatric therapeutics through preclinical and clinical drug trials that lead to drug-labeling changes. Although significant advances have been made in the understanding and management of asthma in adults with appropriately labeled medications, less information is available on the management of asthma in children. Indeed, many medications are inadequately labeled for use in children. In general, the younger the child, the less information there is available to guide clinicians. Because asthma often begins in early childhood, it is incumbent on us to continue to address the primary questions raised in this review and carefully evaluate the medications used to manage asthma in children. Meanwhile, continued efforts should be made in defining effective strategies that reduce the risk of exacerbations. If the areas of defined need are addressed in the coming years, namely prevention of exacerbations and progression of disease, as well as primary intervention, we will see continuing reduction in asthma mortality and morbidity along with improved quality of life for children with asthma. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

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The Eunice Kennedy Shriver National Institute of Child Health and Human Development convened an Asthma Group in response to the Best Pharmaceuticals for Children Act. The overall goal of the Best Pharmaceuticals for Children Act Program is to improve pediatric therapeutics through preclinical and clinical drug trials that lead to drug-labeling changes (http://bpca.nichd.nih.gov). The task of the Asthma Group was to discuss differences between childhood and adult asthma to define specific knowledge gaps related to current asthma management. Two broad issues were discussed: (1) challenges with drug delivery in children, especially in relation to age, and (2) differences in outcome measures between pediatric and adult studies.

The Asthma Core Group evaluated these issues over the past year by (1) developing responses to high-level questions on disease progression and manifestation in children and adults; (2) summarizing individual responses in each area in regard to

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Abbreviations used
CO: Carbon monoxide
EBC: Exhaled breath condensate
FENO: Fraction of exhaled nitric oxide
HRV: Human rhinovirus
RBM: Reticular basement membrane
RSV: Respiratory syncytial virus
SARP: Severe Asthma Research Program

cause, diagnosis, pathophysiology, outcomes, and therapeutics; (3) identifying and justifying major issues, knowledge gaps, and short- and long-term objectives in each area; and (4) summarizing these observations for this report.

These findings are presented in 4 broad areas: natural history and pathophysiology, diagnostics and biomarkers, outcome measures, and therapeutics. Each section summarizes the relevant issues, identifies the important information gaps, and presents short- and long-term objectives to fill identified gaps. The section on therapeutics further identifies 4 classes of drugs that merit close attention because of the frequent use and lack of appropriate dosage information by age. This information is intended to inform future studies by the National Institutes of Health, the US Food and Drug Administration, and pharmaceutical firms to advance pediatric asthma care.

NATURAL HISTORY AND PATHOPHYSIOLOGY

Asthma, which typically begins in childhood and occurs throughout life, has common clinical manifestations but many different "phenotypes" that are associated with variable disease courses. Not all children who wheeze early in life will have asthma later in life.[1] Sex also influences the natural history of asthma, with a shift in severity and prevalence biased toward women after puberty.[2] In this section differences across the ages in natural history and pathophysiology as they relate to the inception, progression, and exacerbations of asthma are reviewed (Table I).

Inception of asthma

Asthma results from the interaction between the host's genetics and environment. Exposures to environmental stimuli lead to alterations in inflammatory pathways that trigger wheezing illnesses and the development of asthma. Birth cohort studies have identified risk factors (allergic sensitization and wheezing with viral infections) for asthma inception. Allergic sensitization early in life is an important risk factor for persistent wheezing and asthma development.[1,3-5] Children with multiple early aeroallergen sensitizations are at increased risk of morbidity associated with childhood asthma.[6]

Wheezing with viral infections is the most common presentation of asthma in early life. Preschool children have an intermittent pattern of disease and are often well between episodes. Viruses, human rhinovirus (HRV), respiratory syncytial virus (RSV), influenza virus, and metapneumovirus are identified in approximately 90% of children younger than 3 years with acute wheezing.[3,7] Pathogenic bacteria also might play a role in recurrent wheezing.[8] Wheezing associated with RSV in infancy, particularly those episodes requiring hospitalization, increase the risk of recurrent wheezing and asthma.[9-12] Wheezing associated with HRV has been identified as a strong risk factor for persistent asthma.[3,13] It is unclear whether RSV and HRV cause asthma or uncover an underlying predisposition to disease. However, a recent trial of palivizumab in healthy preterm infants suggests that prevention of severe RSV infection in infancy might prevent recurrent wheeze.[14] Whether these findings hold true for prevention of childhood asthma remains an open and important question.

Intermittent viral infections trigger an exaggerated inflammatory response (Fig 1), which might be present even when symptoms are absent. The eosinophilic predominance seen on bronchoalveolar lavage in older subjects is less pronounced in infants.[15] However, some children might have a noneosinophilic or neutrophilic form of asthma. These patients might not respond to corticosteroids, although it remains controversial whether airway neutrophilia represents a true asthma inflammatory phenotype or whether it represents exposure to higher doses of corticosteroids. Biomarker development to distinguish inflammatory phenotypes in children will be a major advance in the treatment of asthma because it is unclear what predisposes young children to have one asthma phenotype over another. Moreover, the temporal stability of these phenotypes is not understood.

In addition to viral infection and allergen exposure, other environmental factors influence the development of asthma, including maternal depression, psychological stress, and exposure to air pollution. Prenatal and postnatal maternal depression, anxiety, and distress and exposure to psychological stress have been associated with the development of asthma.[16,17] In addition, exposure to both indoor and outdoor air pollution also appears to influence asthma development.[18,19] The relative contribution of each of these environmental factors in the inception of asthma is unknown. It is likely that exposure to a combination of these and other environmental factors at a specific time in the maturation of the immune response in a genetically susceptible subject determines whether asthma will develop.

Progression of asthma

The progression of asthma is variable both between and within subjects. The National Heart, Lung, and Blood Institute's Severe Asthma Research Program (SARP) has focused on the clinical, physiologic, and biologic heterogeneity of asthma. An unsupervised hierarchical cluster analysis of adult SARP participants with the full spectrum of disease allowed for grouping of patients based on similarities free from an *a priori* bias to identify potential clinical asthma phenotypes.[20] Similarly, a cluster analysis of 300 children (ages 6-17 years) identified marked heterogeneity[21] and identified distinct clusters from the SARP adult studies. Although distinct clinical phenotypes were identified, the airway inflammatory response underlying those phenotypes is less distinct. Most asthmatic patients have some form of airway remodeling regardless of phenotype. Remodeling, which is characterized by epithelial cell injury, thickening of the reticular basement membrane (RBM), subbasement fibrosis, smooth muscle hypertrophy and hyperplasia, and angiogenesis, is presumed to result in abnormalities in lung function, including persistent airflow limitation and increased airway hyperresponsiveness. Airflow obstruction might be permanent or only partially reversible. Lung function changes seen in children are different than those seen in adults who experience a loss of lung function over time. In children 5 to 11 years old, the magnitude